Mayer-Rokitansky-Küster-Hauser Syndrome*

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ABSTRACT

Mayer-Rokitansky-Küster-Hauser (MRKH) Syndrome is a rare disease found in 1:4,000-5,000 live female births. It presents with vaginal and uterine agenesis in females. Ultrasound of the pelvis is the initial imaging of choice. Pelvic Magnetic Resonance Imaging (MRI) is the gold standard to confirm the presence of a rudimentary uterus. Surgical and nonsurgical options to create a neovagina may be offered to the patient. Counselling of patients is necessary.

This report presents a case of a 15-year old phenotypic female with cyclic abdominal pain subsequently noted with absent vaginal canal. Ultrasound and MRI of the pelvis showed the absence of a uterus and upper vagina with intact ovaries. Karyotyping showed 46, XX, confirming that the patient is a female. Analgesics were prescribed for the abdominal pain. Regular counselling was provided by Adolescent Medicine.

Keywords: vaginal agenesis, uterine agenesis, primary amenorrhea, adolescent

INTRODUCTION

Mayer-Rokitansky-Küster-Hauser syndrome (MRKH), or Müllerian agenesis was first described by German anatomist and physiologist Mayer in 1829 as part of multiple congenital anomalies among four stillborns. In 1961, the term "rudimentary solid septate uterus with solid vagina" was coined as the Mayer-Rokitansky-Küster Syndrome by Hauser.[1] Hauser and Schreiner studied this further and emphasized the importance of distinguishing between Müllerian agenesis and testicular feminization (androgen insensitivity), both of which present with vaginal atresia.[2]

This report presents a case of a patient with MRKH presenting as recurrent hypogastric pain. Clinical presentation, diagnosis, pathophysiology, and management of MRKH will be discussed.

CASE REPORT

A 15-year old female, Filipino, presented with cyclic hypogastric pain. History started eight months prior, when she complained of crampy, non-radiating hypogastric pain, with pain scale of 8 out of 10 in severity lasting 2 hours for 2 days each month. The pain spontaneously resolved with rest. There were no associated fever, abdominal distention, vomiting, or bowel and bladder changes. It interfered with her school activities leading to frequent missed school days.

The monthly occurrence of abdominal pain prompted consult with a general pediatrician and was referred to a gynecologist. Physical examination revealed an absent vaginal canal. Transrectal ultrasound showed prepubertal anteverted uterus with thin endometrium (Appendix A). She was assessed as a case of imperforate hymen and was advised surgery. They went to a tertiary pediatric hospital for further evaluation and counselling.

Thelarche and pubarche were at 12 years of age. Axillary hair and acne were noted at 13 years of age. She has had no menarche. She denies history of oral contraceptive intake. There was no note of excessive facial hair or deepening of voice. She is a nulligravid with no prior sexual encounters. She had expressed desires to have a family of her own in the future. All the females in their family have a history of menstruation and are able to bear children. There was no known family member with a similar case as the patient.

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Upon examination, the patient was seen awake and not in cardiorespiratory distress. She had stable vital signs and reported no pain at the time of examination. Her weight is 38 kg, and she is 155 cm tall ($z < 0$), with a normal BMI for age of 15.8 kg/m^2 ($z = -2$). The abdomen was flat with normoactive bowel sounds and tympanitic on percussion. There were no palpable abdominal masses, organomegaly, or tenderness. On gynecologic examination, the patient was noted to have a grossly normal female external genitalia with no discharge or bleeding (Appendix B). Pubic hair was present. The vaginal canal could not admit a cotton swab. The Sexual Maturity Rating (SMR) was stage 3 for pubic hair and stage 3 for breast.

She was seen at the General Pediatrics outpatient department (OPD), assessed as a case of imperforate hymen. She was then referred to Pediatric Gynecology service for further assessment and management. Rectal ultrasound showed prepubertal uterus, multicystic both ovaries, no adnexal masses, no hematometria, and no free fluid in the cul-de-sac (Appendix C). Vaginal agenesis was considered, hence pelvic Magnetic Resonance Imaging (MRI) and karyotyping were requested. The patient was prescribed with ibuprofen and celecoxib for the hypogastric pain.

Pelvic MRI plain and contrast findings showed no normal-looking uterus or cervix, with a consideration of agenesis, with multi-cystic ovaries, bilateral and no gross pelvic masses (Appendix D). Karyotyping showed 46, XX, normal female karyotype (Appendix E). The impression was MRKH syndrome. She was advised for close follow-up and to continue analgesics as needed. She was referred to Adolescent Medicine for counseling. Plans for surgical management were discussed.

CASE DISCUSSION

Evaluation of abdominal pain in adolescent females is challenging. A thorough history and physical examination narrows down the differentials. The initial step to the diagnosis is to obtain from the history the duration, frequency, location, and intensity of abdominal pain. Patients with acute abdominal pain usually presents with a single episode that may last from hours to days. On the other hand, patients with chronic abdominal pain typically complains of pain that lasts from days to months.[3]

Reported was a female adolescent who complained of crampy, cyclic abdominal pain lasting for eight months. Location of chronic abdominal pain in a female adolescent will limit the differential diagnoses. In this case, the abdominal pain was confined to the hypogastric area. Organic causes of hypogastric pain may involve the intestinal, urinary, reproductive, and muscular systems. A gastrointestinal, urinary, or infectious cause was least likely in the absence of bowel or bladder changes, and fever. Muscular strain is excluded given a negative history of trauma or exertion. Pregnancy was considered as the patient was of reproductive age. However, this is improbable with the history of amenorrhea.

The American College of Obstetrics and Gynecology defines primary amenorrhea as the absence of menarche by age of 15 years or within 3 years of thelarche.[4] An evaluation for primary amenorrhea is warranted in this patient as she was amenorrheic for 3 years after thelarche at the age of 12.

Evidence of female secondary sexual characteristics indicates normal functioning hormones. Therefore, the likelihood is low for a hypothalamic, pituitary, or ovarian problem. Several differentials may be considered in a patient presenting with primary amenorrhea and normal secondary sexual characteristics.

Androgen insensitivity syndrome (AIS) is a mutation of the gene for androgen receptor. The complete form of this disease affects genotypic males and presents with female external genitalia, blind vagina, absent uterus and adnexa, and undescended testes.[5] Patients with AIS do not grow axillary or pubic hair differentiating it from patients with MRKH syndrome. Further evaluation with medical imaging is necessary to determine the presence and type of gonads as well as abnormalities in the uterine and vaginal outflow tract.

Ultrasonography is the first-line diagnostic imaging test for the identification of pelvic structures. It may or may not identify anomalies of other pelvic organs that are associated with MRKH syndrome.[2] It has a sensitivity of 44%, and a high specificity of 98%.[6] Pelvic MRI can determine exact anatomic characteristics of MRKH syndrome. It has a sensitivity of 81% and specificity of 100%.[7] It is performed when ultrasound findings are inconclusive. MRI provides an accurate evaluation of uterine aplasia and a clear visualization of the rudimentary horns and ovaries.[8] In this case, pelvic MRI confirmed uterine and vaginal agenesis with the presence of ovaries.

Karyotyping identifies the patient's genotype and conclusively differentiates between AIS and MRKH syndrome.[5] The patient in this case had normal female 46, XX karyotype. With the findings of normal female secondary sexual characteristics and radiographically confirmed uterine and vaginal agenesis, the diagnosis of MRKH Syndrome was concluded.

Patients with MRKH syndrome have normal female phenotype, thelarche, pubarche, and karyotype (46,XX) but present with primary amenorrhea. The extent of malformations in MRKH syndrome varies widely. There are three classifications of MRKH.[9,10] Typical MRKH (Type I) presents with isolated utero-vaginal agenesis and is the most common among the types.[1] Atypical MRKH (Type II) exhibits utero-vaginal agenesis with asymmetrical malformations of the fallopian tubes, ovaries, or renal systems. The third type is Müllerian aplasia, Renal aplasia, and Cervico-thoracic Somite dysplasia (MURCS). Other ancillary tests may be done to identify the presence of anomalies commonly associated with MRKH syndrome. The patient did not clinically present with other anomalies, therefore she was classified as having typical or Type I MRKH.

Since 1917, there have been only three practice- or hospital- based studies on the prevalence of MRKH syndrome estimating it at around 1 in 4,000-5,000 females.[11,12,13] In the ICD-10 registry, the diagnosis of MRKH syndrome does not have its own category. Instead, it belongs under the codes Q51.0 (agenesis and aplasia of uterus) and Q52.0 (congenital absence of vagina). The Philippine Pediatric Society registry reported 3 cases of congenital absence of vagina and 4 cases of agenesis and aplasia of the uterus.[14]

The maturation of the female reproductive organs is a complex process that can be summarized into three stages: Müllerian duct formation, Wolffian duct regression, and Müllerian duct differentiation. By the 8th week of gestation, the Sex-determining Region Y (SRY) gene triggers androgen and anti-Müllerian hormone production in male gonads. This suppresses the Müllerian ducts and stimulates the Wolffian ducts to produce a male phenotype. In the absence of the SRY gene, the Müllerian duct is uninhibited and triggers differentiation to the uterus, fallopian tubes, cervix, and vagina.[15] MRKH syndrome is an anomaly in the Müllerian duct differentiation of the female reproductive organs. The etiology of MRKH syndrome is not fully understood. However, there have been studies on the genetic abnormalities that contribute to its development, such as ESR1, OXTR, HOXA10, and HOXA 13.[15] There is no definite or specific gene known to be involved in MRKH.

Patients with MRKH syndrome may present with cyclic abdominal pain. This is commonly due to a functioning endometrium in a rudimentary uterus. Another consideration is endometriosis via a metaplastic process in peritoneal mesothelium or ovarian surface endothelium referred to as coelomic metaplasia.[17] The cyclic hypogastric pain in this case may be interpreted as menstrual cramps. Nonsteroidal anti-inflammatory drugs (NSAIDs) are appropriate as first-line treatment.[18]

MRKH syndrome has implications to a woman's self-esteem. The diagnosis should be disclosed sensitively. Counselling and psychological support is important at the point of diagnosis and thereafter.[19] Infertility was found as the hardest psychological aspect of the condition to accept. This should be acknowledged during disclosure and services should be offered in exploring and alleviating such issues.[20] A multidisciplinary team approach involving the General Pediatrician, Adolescent Medicine, Psychiatry, and Gynecology services is ideal.[19]

The patient is at middle adolescence. Counseling is centered on the individuation process where self-identity is established. During these sessions, normality in the sexual body is discussed as well as the implications of her condition on the impairment to experience sexual pleasure, to sexual intercourse, and to conceive children. As she proceeds to late adolescence, she is guided to

progressively accept her condition through intellectualization. Acquiring more knowledge about her condition allows her to feel more in control. As the patient is transitioning to adulthood, a supportive network should be established, composed of adult family members, peers, and health care providers.[19]

Risks and benefits of surgical interventions are discussed once the patient is psychologically fit to undergo surgical intervention. Treatment options for MRKH syndrome include vaginal dilation as the first line management for vaginal agenesis. This procedure has a success rate of 75-85%.[21,22] Minimally invasive advances have been developed in creating a neovagina. Two of the most common procedures being practiced today are the Vecchietti and the Davydov procedure.[23,24]

MRKH syndrome has great impact on fertility. Before the advent of reproductive technologies, patients were limited to adoption.[25] In Vitro Fertilization (IVF) and surrogacy are some relatively new options that can be explored. Petrozza et al. found a 65% success rate of IVF among women with congenital absence of vagina and uterus.[26] None of the female births were noted to have congenital absence of uterus and vagina. To this day, there has been no study showing the hereditary nature of MRKH syndrome.

CONCLUSION

MRKH syndrome is a rare anomaly seen among females presenting with primary amenorrhea and normal secondary sexual characteristics. Imaging of the pelvis is vital to confirm uterine or vaginal agenesis. Psychological management is of utmost importance as the adolescent faces the challenges of infertility and acceptance of this condition. Surgical and nonsurgical options to create a neovagina are treatment options. In-vitro fertilization and surrogacy are offered to women who wish to bear children.

This report is a case of a 15 year-old female presenting with cyclic hypogastric pain. She had normal secondary sexual characteristics and absent vaginal canal. Ultrasound and MRI showed a rudimentary uterus and absent upper vagina with intact ovaries. Karyotyping showed 46, XX, confirming that the patient is a female. Analgesics were given for abdominal pain. Regular counseling is provided by an Adolescent specialist. The best approach in treatment is taken into consideration towards the patient's transitioning to adulthood.

APPENDIX A

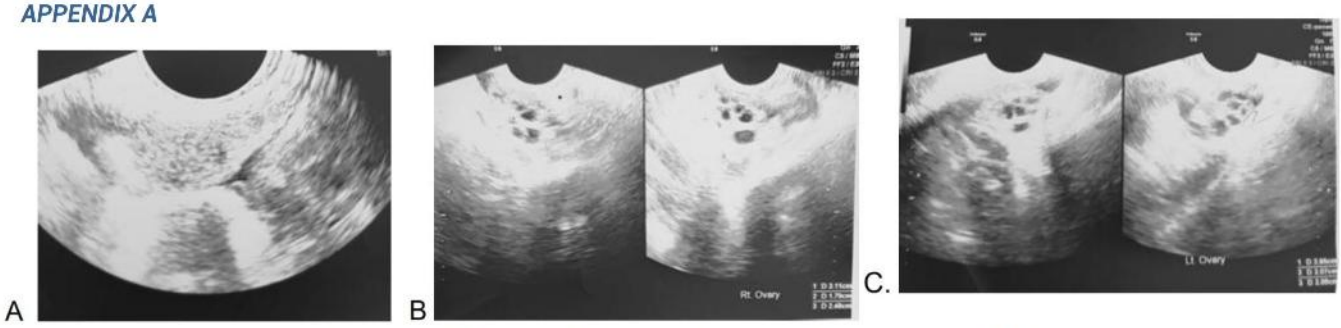

Figure 1. Transrectal ultrasound images. A: Uterus. B: Right ovary. C: Left ovary.

Uterus: 1.93 x 1.50 x 1.16 cm, anteverted
Endometrium: thin, 0.29 cm, hyperechoic
Right ovary: 3.11 x 2.48 x 1.79 cm
Left ovary: 2.85 x 2.09 x 2.07 cm
Cervix: 0.79 x 1.02 x 0.71 cm
No free fluid in the cul de sac

Impression:
Prepubertal anteverted uterus
Thin endometrium
Normal both ovaries

APPENDIX B

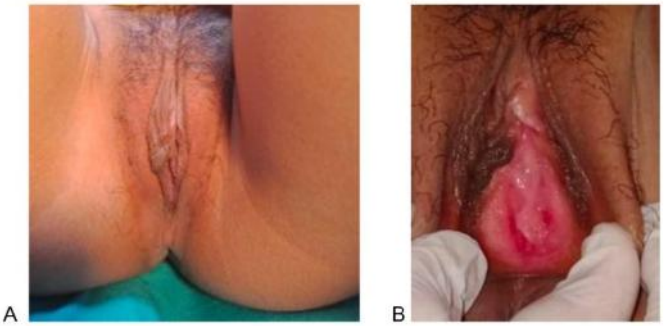

Figure 2. Gynecologic examination. A: External genitalia. B: Vaginal opening demonstrating a blind vagina

APPENDIX C

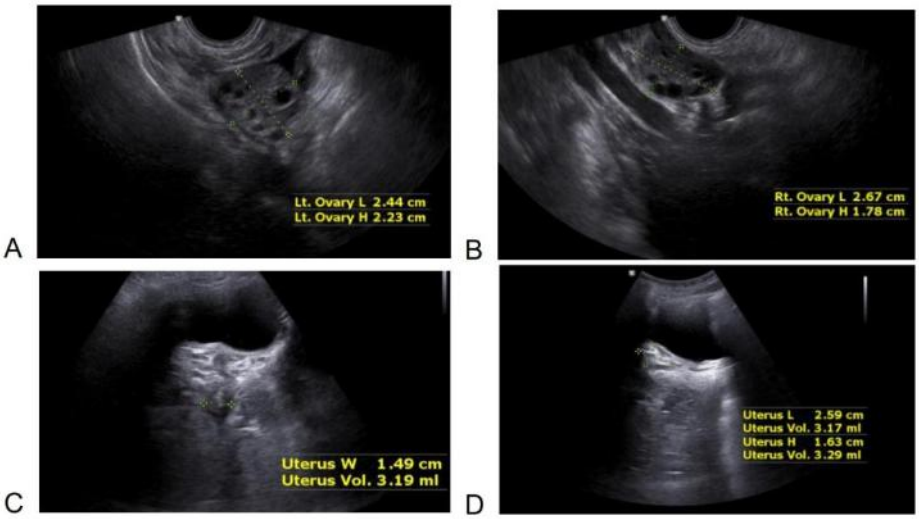

Figure 3. Transrectal ultrasound images. A: Left ovary. B: Right Ovary. C & D: Uterus.

Prepubertal uterus
Multicystic both ovaries
No adnexal masses seen
No heatometria
No free fluid in the cul-de-sac

APPENDIX D

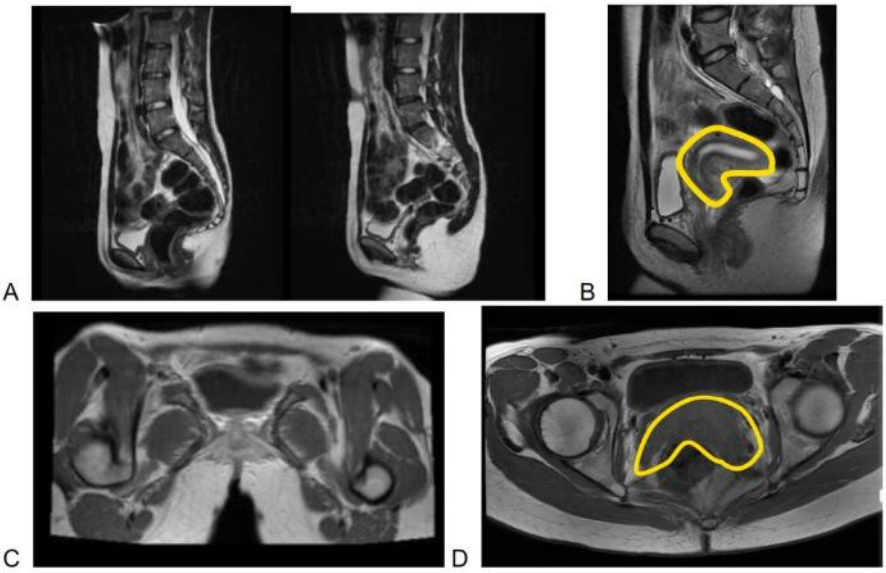

Figure 4. Pelvic MRI plain and contrast. A: Patient, T2-weighted sagittal view. B: Normal, T2-weighted sagittal view demonstrating the presence of a uterus. C: Patient, T1-weighted axial view. D: Normal, T1-weighted axial view demonstrating the presence of a uterus.

Uterus: no normal-looking uterus or cervix visualized. No pelvic masses noted.
Ovaries: multiple small cysts are noted in the right (2.4 x 1.3 cm) and left (2.5 x 1.9 cm) ovaries. No adnexal masses noted.
Urinary bladder: unremarkable.
Bowels: visualized bowels are unremarkable.
No other remarkable findings.

Impression:
No normal-looking uterus or cervix, consider agenesis
Multicystic ovaries, bilateral
No gross pelvic masses

APPENDIX E

Metaphase Counted:	15	**Banding Technique:**	G-Banding	**Number of Cultures:**	2
Metaphase Scanned:	30	**Band Resolution:**	≥ 450		
Metaphase Analyzed:	5	**Additional Method:**			
Metaphase Karyotyped:	3				

ISCN RESULT: **46,XX**
Normal Female Karyotype

CASE COMMENTS:

Chromosome analysis revealed a NORMAL female chromosome complement in all 50 cells examined. There was no evidence of a chromosome abnormality within the limits of current technology.

With a total of 50 metaphase cells examined, this should exclude mosaicism of greater than 6% at a 95% confidence interval (Am J Hum Genet 29:94-97, 1977) in this tissue.

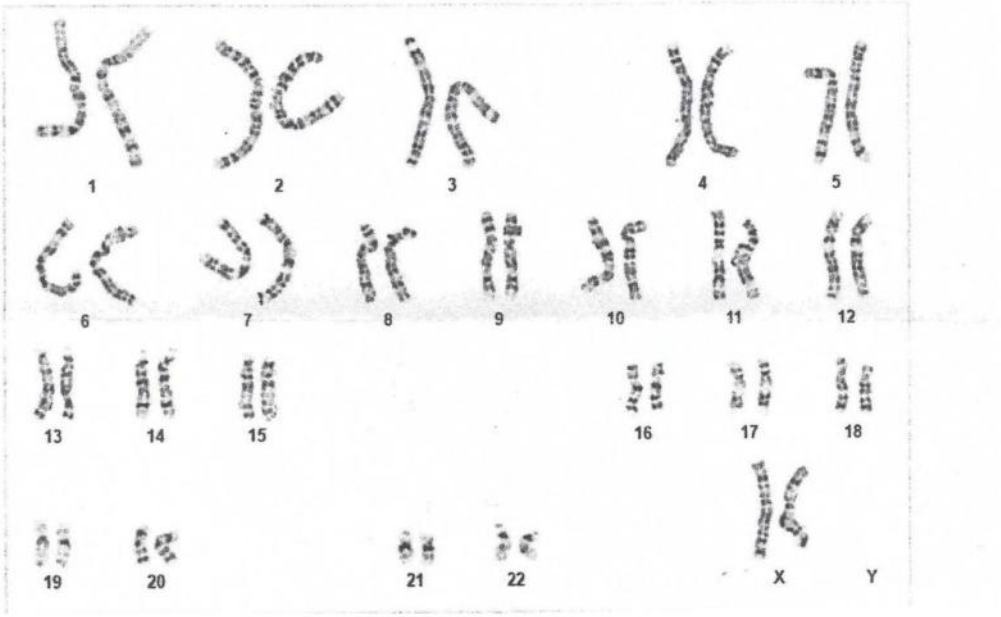

Figure 5. Karyotyping of the patient showing 46,XX, normal female karyotype.